COOPERATIVE AGREEMENT NO: DAMD17-92-V-2007

TITLE: HEMORRHAGIC FEVER WITH RENAL SYNDROME (HFRS) AND INFECTIOUS DISEASES OF MILITARY SIGNIFICANCE IN KOREA

PRINCIPAL INVESTIGATOR: Ho Wang Lee, M.D., Ph.D.

CONTRACTING ORGANIZATION: Korea University
Institute of Viral Diseases
126-1 Anamdong 5-Ga, Seongbuk-Ku,
Seoul 136-075, Korea

REPORT DATE: June 21, 1993

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research, Development, Acquisition and Logistics Command (Provisional), Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

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Accession For	
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Dist	Avail and/or Special
A-1	

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	06/21/93	Final 17 Feb. 92 - 16 June 93

4. TITLE AND SUBTITLE
Hemorrhagic Fever with Renal Syndrome (HFRS) and Infectious Diseases of Military Significance in Korea

5. FUNDING NUMBERS
C-DAMD17-92-V-2007

6. AUTHOR(S)
H.W. Lee and J.D. Arthur

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Institute of Viral Diseases, Korea University
126-1 Anamdong 5-Ga, Seongbuk-Ku,
Seoul 136-075, Korea

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research, Development, Acquisition and Logistics Command (Provisional), ATTN: SGRD-RMI-S
Fort Detrick, Frederick, MD 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for Public Release;
Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

Studies were conducted throughout Korea to better characterize the distribution of militarily important human infections. Antibodies to hantaviruses were demonstrated in 12-15% of urban and rural civilian adults; antibodies to scrub and murine typhus were detected in 11% and 45%. No antibodies to hepatitis A were detected in 40% of rural males age 20, 35% of ROK Military Academy cadets, and 20% of ROKA recruits surveyed. Examination of serum specimens from civilian and ROK military patients admitted with hemorrhagic manifestations continue to show that HFRS usually accounts for less than half of etiologic diagnoses, and the etiology remains unknown in a substantial portion. Most HFRS disease continues to occur in the fall, however a small number of cases occur throughout the year. Urban transmission of scrub typhus was recognized in rapidly developing areas, suggesting that R tsutsugamushi-infected chigger mites may persist with their rodent hosts in areas where urban development encroaches on former scrub habitat. An extensive geozoological survey found the risk to humans of acquiring a HTNV infection is highest in grassy or scrub areas.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Hantavirus, murine typhus, scrub typhus, spotted fever, leptospirosis, seroepidemiology, hepatitis, geozoological survey	24
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	UL

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

Summary

Seroprevalence of antibodies to hantaviruses, rickettsiae, and hepatitis viruses was determined in sera collected during community health surveys in rural areas surrounding Chorwon near the "Iron Triangle" northeast of Seoul, and Chinchun southeast of Seoul; and in city government employees in Kanghwa northeast of Seoul. The prevalence of antibodies to hantaviruses in comparable age groups (≥30 yrs) was similar in each area (ranging from 12.3 - 14.6%). Antibodies to scrub and murine typhus were detected in 11% and 45% of the same age group respectively. Forty percent of males age 20 remained susceptible to hepatitis A. Overall prevalence of antibodies to hepatitis B surface antigen was 60% (B core antibodies were present in 35% reflecting wide routine use of hepatitis B vaccine); surface antigenemia present in 17%. Prevalence of antibodies to hepatitis C in adults was 2.5 - 3.2%.

From 2551 serum specimens from civilian patients with hemorrhagic manifestations examined at the Institute for Viral Diseases in 1992, 429 cases of HFRS, 260 cases of scrub typhus, 187 cases of murine typhus, 22 cases of spotted fever and 4 cases of leptospirosis were confirmed. The etiology remained unknown in 65% of patients. Most patients were identified in Seoul city and the northern and south-western provinces of South Korea. Most cases of HFRS, murine typhus, scrub typhus and leptospirosis occurred in the fall, however small numbers of cases occurred throughout the year.

Of 520 patients admitted to Capitol Armed Forces General Hospital between 1989 - 1993 with possible hemorrhagic fever with renal syndrome, 259 (49.8%) were confirmed to have HFRS; 13 (2.5%) had scrub typhus; 10 (1.9%) had leptospirosis; and 238 (45.8%) had no etiologic diagnosis for their febrile illness. Five of the 238 had a two-fold rise in antibodies to Colorado tick fever-like virus (not sufficient to verify current CTF infection).

Soldiers in ROK Army less than 6 months had a lower rate of detecable antibodies to hepatitis A (78.5%) than soldiers who had served 24 months (83.2%) which suggests there may be some low-level transmission of hepatitis A unrecognized in ROK soldiers. Antibodies to hepatitis B surface antigen were detected in 27% of the soldiers; hepatitis B surface antigen was detected in 6.4% of soldiers serving less than 6 months and 3.3% of soldiers serving 24 months (Chi square = 5.95, power 69%, odds ratio 1.98 [95% confidence interval 1.13 - 3.45]).

Scrub typhus transmission in an urban setting was recognized in rapidly developing Chinhae and Koje Island. R tsutsugamushi-infected chigger mites may persist with their rodent hosts in areas where urban development encroaches on former scrub habitat, posing an ongoing transmission risk of scrub typhus to humans. Therefore, we recommend that scrub typhus be considered in patients who

present in the fall in Republic of Korea with abrupt fever, chills, headache and rash, even though they have no known exposure to scrub habitat.

A total of 1,675 mammals were collected during the geozoological survey. The majority of mammals trapped were Apodemus agrarius: the majority were trapped and most of the rodent burrows were observed in grassy and scrub areas. During the fall, Apodemus populations expand dramatically to provide enough individuals to overwinter. This expansion of Apodemus populations also corresponds to the fall HTNV epidemic season. Adult males are seropositive to HTNV more than twice as often as females (OR 2.6 [1.6-4.5], $p<0.001$): no juvenile and few sub-adults had HTNV antibodies. These data suggest that in-utero, post partum or transmission by milk does not play a role in the maintenance of the virus in Apodemus and that aerosol or arthropod transmission is not the primary route of infection in nature. The risk of acquiring a HTNV infection is highest in grassy or scrub areas but there is a risk to military personnel in any habitat, anywhere within ROK.

TABLE OF CONTENTS

INTRODUCTION

Background

The ecology of South Korea has changed markedly since the end of hostilities in 1954. Reforestation, resumption of organized farming, and human encroachment have altered the human/rodent relationship with resultant alteration in human exposure to infectious agents maintained either directly or indirectly by rodent hosts. HW Lee and colleagues have established the importance of hantaviruses (Hantaan, Seoul, and related viruses) in the causation of widespread human disease in Korea, as well as elsewhere in Asia [1]. Other rodent-borne pathogens, especially leptospirosis and scrub typhus, have only recently been recognized as major health problems in Republic of Korea [2,3]. Studies conducted under USAMRDC grant DAMD-17-92-V-2007 "Hemorrhagic fever with renal syndrome (HFRS) and infectious diseases of military significance in Korea" further elaborated on the importance of these diseases among populations in Korea, including military units, which on initial clinical diagnosis have been confused with HFRS.

Previous Work

The extent of the human disease burden due to leptospirosis in Korea was not well characterized, due in part to the absence of careful scientific investigations in this disease, and to the absence of convenient diagnostic tests to rapidly identify acute infections. Graham has developed a sensitive, specific assay that can rapidly diagnose acute leptospirosis infections, estimate the prevalence of specific antibodies to leptospiral antigens in survey populations, and function well in human pathogenic serovars known to occur in Korea and worldwide.

Although Rickettsia tsutsugamushi was isolated from field mice during the Korean Conflict, little has been done to investigate the epidemiological characteristics of this disease. Scrub typhus was not recognized clinically in Republic of Korea until Lee's report in 1984 [4]. Changes in the ecological conditions in Korea since the Korean Conflict and modifications in agricultural practices suggest that the current disease ecology may be quite different from that observed during investigations made during and after the Korean Conflict.

Colorado tick fever has never been recognized as a human pathogen in Asia: however, the studies above which examined Hantaan seronegative patients with a clinical diagnosis of KHF revealed many sera contained antibodies specific for a virus identical or closely related to CTF. C Calisher of CDC, Fort Collins, confirmed these observations by virus neutralization tests. These suggested that perhaps an heretofore unrecognized viral pathogen exists in Korea which

could be responsible for a portion of the KHF-like clinical disease for which no etiologic diagnosis can be found.

Objectives

To continue to conduct studies throughout Republic of Korea (ROK) to better characterize the distribution of human infections with Hemorrhagic Fever with Renal Syndrome (HFRS) and other infectious diseases of military importance in Korea: to systematically describe the prevalence of infection in rodent and human populations, relating ecology, ectoparasite and rodent population dynamics to transmission and maintenance of infection: and to identify risk factors for acquisition of human disease with the above agents.

MATERIALS AND METHODS

A. Epidemiology

1. Civilian seroprevalence studies.

Sera collected during several community health surveys were submitted to USAMRU-ROK determine the prevalence of antibodies to hantaviruses, rickettsiae, and hepatitis viruses. Surveys were carried out in the rural areas surrounding Chorwon near the "Iron Triangle" northeast of Seoul, and Chinchun southeast of Seoul: and in city government employees (police, teachers, etc) in the Kanghwa area northwest of Seoul. Age and sex data were provided for the specimens from Chorwon and Chinchun.

2. Serum specimens from civilian and military hospitals

Serum specimens from civilian throughout Korea were submitted to the Institute for Viral Diseases for diagnosis of suspected KHF. These specimens were anonymously tested for R tsutsugamushi, R typhi, R siberica and leptospirosis to give additional valuable clues to the spatial and temporal distribution of human pathogens in the Republic of Korea.

3. Capitol Armed Forces General Hospital hemorrhagic fever summary data

Serum specimens from 520 ROK service personnel admitted to hospital between 1989-93 with presumptive diagnosis of hemorrhagic fever were submitted to USAMRU-ROK for etiologic diagnosis. The specimens were analyzed for antibodies to hantaviruses, R tsutsugamushi, R typhi, leptospirosis, and CTF. Risk factors for development of HFRS were reported in final report USAMRDC grant DAMD-17-88-Z- 8042.

4. Serosurveys of ROK Army personnel

ROK AFMC Preventive Medicine department conducted a serosurvey in 3912 active duty ROK Army soldiers in Kyonggi (near the Demilitarized Zone) and Chungnam (central ROK) provinces during a two week period in summer 1991. Sera were processed in the field and brought to USAMRU-ROK for storage at minus 70℃ for later detection of antibodies to Hantaan virus, rickettsiae, leptospirae, CTF, and hepatitis viruses: demographic data were analyzed. Presence of markers to hepatitis infection has been determined in this collection and in 146 ROK Military Academy Cadets since the previous reporting of hantavirus infection prevalence in the report on USAMRDC grant DAMD-17-88-Z- 8042. Rates of antibodies to hepatitis in 600 soldiers who had been in the ROK Army less than 6 months was compared with rates in 600 soldiers with 24 months service (200 soldiers each from city, semi-rural, and rural origin) to see if there was any suggestion of transmission within young military personnel.

5. Urban scrub typhus

Patients with a recent clinical diagnosis of scrub typhus in fall 1991 at the Chinhae Community Hospital were interviewed at their homes to characterize possible disease exposure sites. Charts of patients with a clinical diagnosis of scrub typhus were reviewed for the 1990 and 1991 transmission seasons at the two regional hospitals on Koje Island, adjacent to Chinhae. Population data were provided by the Ministry of Home Affairs. Since the report on DAMD-17-88-Z- 8042, we have determined the prevalence of antibodies to Rickettsia tsutsugamushi and R typhi in hospital-provided random sera remaining after routine clinical laboratory determinations at the four regional hospital clinical laboratories in Chinhae and on Koje Island: sera were obtained in spring and summer (off season for transmission of scrub typhus in ROK).

B. Field Ecology and Microbiology

1. Survey area

A geozoological survey extending throughout the ROK which samples relevant geographical areas in a 50 km grid was completed. Each area was sampled by trap lines which transect all ecological settings at the site. Trapped mammal populations were identified to species and enumerated by age and sex. Meteorological and ecological data was also collected from each site and remains to be analyzed.

2. Collection of field mammals

Field and house rodents were captured by means of baited Sherman and Tomahawk traps [5,6]. The rodents were identified to species and processed under CO2 anesthesia. Serum was collected for serological testing for Hantaan virus, rickettsial agents, and Colorado tick fever (CTF). Tissue samples for isolation of HTNV, scrub typhus, and leptospirosis included lung, kidneys, liver, spleen and lymph node. One kidney was processed in the field for leptospirosis isolation. The rest of the tissue was stored at -70°C. All rodent ectoparasites were collected both in alcohol for identification and frozen for isolation attempts.

3. Taxonomic studies on Apodemus in Korea

A collaborative study was performed with the Carnegie Museum of Natural History in Pittsburgh Pennsylvania. The purpose of this study was to clarify the species and sub-species Apodemus occurring in the ROK. Detailed morphometric measurements and iso-enzyme studies have been done on specimens from selected sites from the geozoological survey and will be completed at the Carnegie.

4. Specimens from patients

Blood, urine or necropsy tissue were collected from acute phase patients for isolation of virus, leptospira, or rickettsia and sera were collected from suspected leptospira, CTF, or rickettsial patients for serodiagnosis. Larger amounts of hyperimmune convalescent serum were collected when possible for experimental purposes.

5. Virus isolation

Details of techniques for isolation of CTF and related viruses in suckling mice and Vero cells have been described previously [7].

6. Leptospiral isolation

Blood, urine or tissue samples were triturated and inoculated into EMJH media as described previously [8]. All positive cultures are identified by standard serological techniques and representative cultures have been sent to the WHO Leptospirosis Laboratory at CDC.

7. Rickettsial isolation

The isolation of scrub typhus from blood, tissue and chigger samples in ICR adult mice has been previously detailed [9]. Isolates were identified by standard serological techniques.

8. Serological tests for leptospiral antibodies

An ELISA for leptospiral IgG and IgM antibodies developed at USAMRIID is being used for serological tests in humans. Since this test is relatively new and the prevalence of different leptospiral serovars, besides Mwogola is presently unknown, a microagglutination test (MAT) [8] is also used in conjunction with the ELISA. Representative serovars from each serogroup are being used. As more serovars are isolated from human and domestic animals studies they will be added to the MAT test to provide a more relevant test.

9. Serological test for rickettsial antibodies.

All serology utilizes established IFAT techniques using yolk sac antigen [10]. Samples are considered serologically positive when the titer is greater than 1:40.

10. Serological tests for CTF like agent

Serological testing for CTF-like agents was done by IFAT [11]; confirmation will be done by plaque reduction neutralization (PRNT).

RESULTS

A. Epidemiology

1. Civilian seroprevalence studies.

a. Cholwon: sera were obtained from 751 individuals ranging in age from 9 to over 70 years (mean 25; 60% <20 yrs). The prevalence of antibodies to hantaviruses was 6.2% overall (≥30 yrs = 14.6%). Scrub typhus antibodies were present in 5% of individuals overall (11% for ≥30 yrs); murine typhus antibodies were present in 19% overall (45% for ≥30 yrs). Overall prevalence of antibodies to hepatitis A virus was 45% with at least 40% of males age 20 remaining susceptible (Figure). Overall prevalence of antibodies to hepatitis B surface antigen was 60% (B core antibodies = 35% reflecting wide routine use of hepatitis B vaccine);

surface antigenemia present in 17%. Overall prevalence of antibodies to hepatitis C was 1.3% (3.2% for ≥30 yrs).

b. Chinchun: sera were obtained from 200 individuals ranging in age from 13 to 71 years (mean 50). The prevalence of antibodies to hantaviruses was 11% (≥30 yrs =13.2%).

c. Kanghwa: sera were obtained from 203 city government employees ranging in age from late twenties through fifties. The prevalence of antibodies to hantaviruses was 12.3%. Scrub and murine typhus antibodies were found in 0.5% and 33% of individuals respectively. Prevalence of antibodies to hepatitis C was 2.5%.

2. Diagnostic serology on specimens submitted by civilian and ROK military hospitals in Korea in 1992

The total number of serum specimens from civilian patients with hemorrhagic manifestations examined for Hantaan virus, Rickettsia tsutsugamushi, R typhi, R Siberica and Leptospirosis at the Institute for Viral Diseases in 1992 was 2551. There were 429 cases of HFRS, 260 cases of scrub typhus, 187 cases of murine typhus, 22 cases of spotted fever and 4 cases of leptospirosis confirmed serologically among these suspect hemorrhagic disease patients. The percentage of serologically confirmed patients among clinically suspected patients are shown in Table 1. It is noteworthy that the etiology of 65% of the clinically suspected hemorrhagic disease patients was unknown by the methods employed in the study.

The geographical occurrence of HFRS, murine typhus, scrub typhus, spotted fever and leptospirosis is shown in Table 2. The majority of the hemorrhagic disease patients were identified in Seoul city, Kyunggido, Kangwondo, Chungcheongdo, and the northern and south-western parts of South Korea. Sex and age distribution of hemorrhagic diseases is shown in Table 4. The total number of HFRS patients confirmed serologically at Korea University Institute of Viral Diseases, Seoul National University College of Medicine, NIH Korea, Korea Green Cross Hospital and US Army Medical Research Unit/Korea in 1992 was 1167 as shown in Table 5. Details of geographic and seasonal occurrence of HFRS in 1992 are shown in Tables 6 and 7. Outbreaks of HFRS, murine typhus, scrub typhus and leptospirosis occurred in the fall of 1992 during epidemic season of HFRS; however small number of patients occur throughout the year.

3. Capitol Armed Forces General Hospital hemorrhagic fever summary data.

Of 520 patients admitted to Capitol Armed Forces General Hospital between 1989 - 1993 with possible hemorrhagic fever with renal syndrome, 259 (49.8%) were confirmed to have HFRS: 13 (2.5%) had scrub typhus: 10 (1.9%) had leptospirosis: and 238 (45.8%) had no etiologic diagnosis for their febrile illness. Five of the 238 had a two-fold rise in antibodies to Colorado tick fever-like virus (not sufficient to verify current CTF infection): 33 individuals without current etiologic diagnosis had evidence of prior infections (HTNV = 5: scrub typhus = 4: and leptospirosis = 24). It is notable that the patients admitted to Capitol Armed Forces General Hospital with presumptive diagnosis of HFRS are much more likely to be proven to have HFRS than patients being seen in the civilian community.

4. Serosurveys of ROK Army personnel

Sera were obtained from 3912 active duty ROK Army soldiers during a two week period in summer 1991: 1900 in Kyonggi-do (near the Demilitarized Zone) and 2012 in Chungnam-do (central ROK) provinces. Mean age of the soldiers was 21.5yrs (range 18-47yrs): the 107 officers were older than the 3805 enlisted (25.8yrs versus 21.4yrs).

Seroprevalence for hantavirus antibodies was 1.6% (3/107 officers [2.8%] and 59/3805 enlisted [1.55%], p=NS: geometric mean titer = 1107). IgM antibodies to hantavirus were detected at >1:100 dilution (GMT = 419) in the sera of 15 of these 62 soldiers. Two of the soldiers with IgM antibody had KHF and were included in the case-control study, one had received Hantavax, and 8 of the remaining 12 who could be contacted had no known febrile illness of consequence during the previous two years.

Soldiers whose origin was rural were seropositive for hantavirus antibodies more often than soldiers of urban origin (25/930 [2.7%] versus 37/2944 [1.26%], p<0.005). Seropositivity to hantavirus was significantly related to age, rank, and length of service (latter two are markers for age). We conclude that prevalence of pre-existing antibodies to hantaviruses in ROK soldiers is sufficiently low, even in soldiers from rural areas, that pre-screening soldiers would not be necessary in the event that ROKA wished to administer KHF vaccine at some future date.

Soldiers in ROK Army less than 6 months had a lower rate of detectable antibodies to hepatitis A than soldiers who had served 24 months (471/600[78.5%] vs 499/600[83.2%]: Chi-square = 4.22, power = 54%) which suggests there may be some low-level transmission of hepatitis A unrecognized in ROK soldiers: there was no significant difference in rates between soldiers of city, semi-rural or rural origin.

Antibodies to hepatitis B surface antigen were found in approximately 27% of the soldiers. Hepatitis B surface antigen was detected in 6.4% of soldiers serving less than 6 months and 3.3% of soldiers serving 24 months

(Chi square = 5.95, power 69%, odds ratio 1.98 [95% confidence interval 1.13 - 3.45]). Hepatitis B vaccine has been used widely in Korea and probably accounts for a sizeable portion of those soldiers who test positive to antibodies to surface antigen.

ROK Military Academy cadets were similar age to soldiers, but their rate of antibodies to hepatitis A was notably lower (93/146[64%]), demonstrating a more substantial cohort of non-immunes than appreciated within Korean medical circles.

5. Urban scrub typhus

Eight recently recovered scrub typhus patients were visited at their homes in Chinhae and on Koje Island. All 8 lived in an urban setting; two lived in high-rise apartment complexes. Three patients recalled no activity that might bring them into contact with chigger mites: one was a shipyard worker, one picnicked on a small patch of grass adjacent to her apartment and one only walked a dirt path across a vacant lot to market near her house. Five thought their exposure occurred while working in small garden plots or golfing. One 3x5m garden plot was within the home wall; the others were grouped in small vacant lots between buildings. (Ancestral burial mounds are typically grassy areas in cleared scrub on the periphery of urban as well as rural settlements. Visiting these sites and picnicking on the grass is common family practice after the summer rains are over).

Seventeen Apodemus agrarius trapped in the immediate vicinity of the patients' homes in December had serum antibodies to Rickettsia tsutsugamushi. No Rattus spp were trapped.

140 patient records were reviewed (51 from 1990; 89 from 1991); 91 from Okpo-Daewoo Hospital, Jangseungpo-shi, and 49 from Koje Christian Hospital, Koje-gun. The Okpo-Daewoo Hospital, built 9 years ago, serves one-tenth of the land mass and one-half of the population of Koje Island in the rapidly developing Jangseungpo city; the population served are mostly shipyard and company workers. Koje Christian Hospital serves the remainder of the island with long established farm lands and small suburban communities; about half the families served are farmers. Incidence overall was 63 cases/100,000 population/year for 1991 (114/100k/yr Jangseungpo-shi and 35/100k/yr Koje-gun). The majority of cases occurred from mid-October to mid-November (range end-September through second week in December); one case occurred early August and 2 cases occurred the first week of January. Forty-six percent of patients were male and 54% were female; mean age 38.4 (range 1.3-80 yrs). Mean prodrome length reported was six days (1-17d); a rash was noted in 115 (82%); an eschar in 93 (66%); and regional lymphadenitis in 8 (6%). Hospitalization duration ranged from one to nineteen days (mean 5.1, mode 4); patients over 50 years of age were more likely to be hospitalized

five or more days (odds ratio =4.5 [95% confidence interval 1.9-11]): there was no association between the length of prodrome and hospitalization duration. Hepatitis was the admitting clinical diagnosis in 28 patients (20%). There were no deaths.

The four hospitals provided 1264 serum specimens for testing: age (mean 38 yrs) and gender distribution were not significantly different between hospitals. Seropositivity for scrub typhus antibodies was most significantly related to age (3.6% increase per year of age increase [95% CI 2.6-4.7]). Seroprevalence of antibodies to R tsutsugamushi by location was 7%(46/653) for Chinhae Jeil and 21%(15/71) for Chinhae Hyundai hospitals (p<0.001): and 24%(77/324) for Koje Daewoo and 14%(31/216) for Koje Christian hospitals (p=0.01): or 8.4% and 20% for the combined Chinhae and Koje Island hospitals respectively (p<0.001) (Table 8). Seroprevalence of antibodies to Rickettsia typhi was 23%(151/653) for Chinhae Jeil and 35%(25/71) for Chinhae Hyundai hospitals (p=0.04): and 28%(91/324) for Koje Daewoo and 33%(72/216) for Koje Christian hospitals (p=NS): or 24% and 30% for the combined Chinhae and Koje Island hospitals respectively (p=0.03).

Finding a lower seroprevalence of antibodies to R tsutsugamushi from Chinhae Jeil Hospital, serving predominantly families from the well established city-center, compared to Chinhae Hyundai, serving the more peripheral portions of the city, is consistent with Yi's reported exposure in Chinhae. He found older people who work in rural or city-edge garden plots are at highest risk. In contrast we found substantially higher scrub typhus attack and seroprevalence rates in Jangseungpo City than the more rural remainder of Koje Island, which combined with the high prevalence of antibodies to R tsutsugamushi in rodents trapped near patients' homes, confirms that infected mites remain active in areas that are now a city.

Our data show that R tsutsugamushi-infected chigger mites may persist with their rodent hosts in areas where urban development encroaches on former scrub habitat, posing an ongoing transmission risk of scrub typhus to humans. Therefore, we recommend that scrub typhus be considered in patients who present in the fall in Republic of Korea with abrupt fever, chills, headache and rash, even though they have no known exposure to scrub habitat.

B. Field Ecology

A total of 1,675 mammals were collected during the geozoological survey. The species collected and the antibody distribution are detailed in the report on DAMD-17-88-Z- 8042. The majority of mammals trapped were Apodemus agrarius. Identification to sub-species was not possible except in the case of A agrarius mantchuricus. A total of 226 Apodemus have been further processed and the skulls and study skins along with the iso-enzyme

data will be forwarded to the Carnegie Museum for further analysis.

Apodemus were found in all habitats sampled but the majority were trapped in grassy areas and this was where most of the rodent burrows were observed. These areas provide abundant food (various herbaceous products, including seeds) and shelter. During the fall, Apodemus populations expand dramatically to provide enough individuals to overwinter. These grassy areas have numerous species of grasses and herbaceous plants which are seeded out at this time and provide abundant food for the exploding populations. This expansion of Apodemus populations also corresponds to the fall HTNV epidemic season. In many cases, the grassy areas were not associated with agricultural practices such as rice farming. A large number of Apodemus were also found in scrub areas which also provide abundant food and shelter especially in the fall. Apodemus were also found in rice field areas but were usually trapped in areas where there were clumps of grass or reeds to provide shelter and food.

There were no differences between sex or species distribution of Apodemus according to habitat. However, A agrarius mantchuricus was seen more in agricultural areas, such as gardens, than in rice fields.

There was no difference in distribution of scrub typhus seropositivity by sex, as would be expected with an arthropod borne disease. There was also no difference by age since most of the trapping was done in the fall, when chigger mites are active, and all age groups are equally exposed. As expected, most of the scrub positive animals were trapped in the grassy and scrub areas.

Scrub antibody positive Apodemus were found throughout Korea indicating that the disease can be widespread and pose a threat to military personnel throughout the ROK. A total of 12 isolates were made from Apodemus and a total of 5 isolates were made from ROK soldiers. We are in the process of identifying these according to strain.

Distribution of HTNV antibodies in Apodemus populations by age and sex shows that adult males are seropositive more than twice as often as females (OR 2.6 [1.6-4.5], $p<0.001$). There were no antibodies found in juveniles and only a very low prevalence in sub-adults. These data suggest that at least within Apodemus populations in nature, aerosol or arthropod transmission is not the primary route of infection. Also, in-utero, post partum or transmission of virus by milk does not play a role in the maintenance of the virus in Apodemus. The distribution of antibodies according to habitat show that the risk of acquiring a HTNV infection is most likely in grassy or scrub areas but there is a risk in any habitat.

HTNV antibody positive Apodemus were found throughout the ROK indicating that it can pose a threat to military personnel anywhere in Korea. A total of 23 HTNV isolates were made from Apodemus. We are in

the process of analyzing these by PCR and restriction endonucleases to determine if there are strain differences between the different locations. A total of 4 isolates were also made from ROK and US soldiers and these will also be analyzed by PCR.

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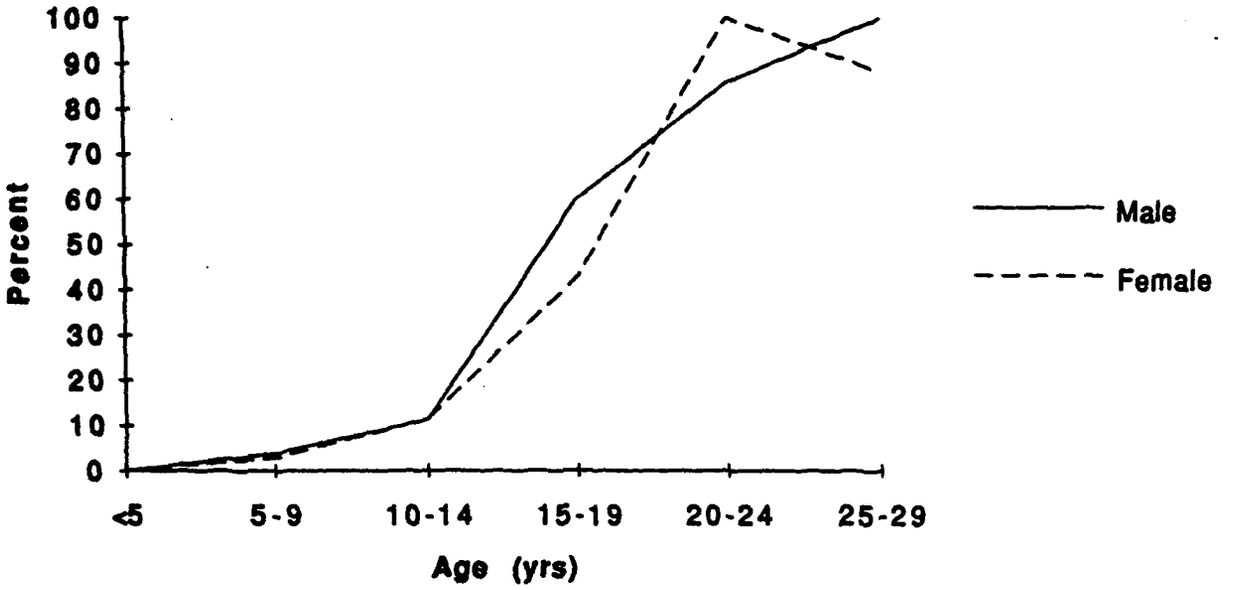

Figure 1.

Seroprevalence of Hepatitis A - Chorwon 1991

Table 1. Patients with hemorrhagic fever with renal syndrome (HFRS), murine typhus, scrub typhus, spotted fever group (SFG) rickettsiosis and leptospirosis diagnosed serologically among specimens from suspect hemorrhagic fever patients submitted to Institute of Viral Disease, Korea University in 1992

Disease	Civilians	% positive
HFRS	429	17
Scrub typhus	260	10
Murine typhus	187	7
SFG rickettsiosis	22	0.8
Leptospirosis	4	0.2
Unknown	1649	65
Total tested	2551	100

Table 2. Geographical distribution of HFRS, murine typhus, scrub typhus, spotted fever group (SFG) rickettsiosis and leptospirosis among civilian suspect hemorrhagic fever patients in Korea, 1992

Province	HFRS	murine typhus	scrub typhus	spotted fever	leptospirosis
Seoul city	144	88	69	9	1
Kyunggi-do	192	47	89	8	2
Kangwon-do	24	11	11	2	0
Chungcheongbuk-do	13	6	12	0	0
Chungcheongnam-do	16	5	32	1	1
Kyungsangbuk-do	1	1	6	0	0
Kyungsangnam-do	1	4	11	0	0
Jeollabuk-do	3	1	8	1	0
Jeollanam-do	8	5	11	1	0
Jeju-do	0	2	0	0	0
Unknown	27	17	11	0	0
Total	429	187	260	22	4

Table 3. Monthly occurrence of HFRS, murine typhus, scrub typhus, spotted fever group (SFG) rickettsiosis and leptospirosis among specimens from civilian suspect hemorrhagic fever patients submitted to Institute of Viral Disease, Korea University 1992

Month	Sera tested	HFRS	murine typhus	scrub typhus	spotted fever	leptospirosis	unknown
1	120	22	3	1	0	0	94
2	94	19	5	0	0	0	70
3	102	14	2	0	0	0	86
4	126	22	9	1	0	0	94
5	144	32	15	2	2	0	93
6	201	30	9	3	0	1	158
7	207	26	5	3	6	0	167
8	204	27	7	3	2	1	164
9	194	14	9	6	1	1	163
10	350	61	41	97	2	0	149
11	500	93	47	132	9	1	218
12	309	69	35	12	0	0	193
Total	2551	429	187	260	22	4	1649
(%)		(17)	(7)	(10)	(0.8)	(0.2)	(65)

Table 4. Age and sex distribution of HFRS, murine typhus, scrub typhus, spotted fever and leptospirosis confirmed from civilian suspect hemorrhagic fever patient sera submitted to Institute of Viral Disease, Korea University in 1992.

Age	HFRS			murine typhus			scrub typhus			spotted fever			leptospirosis		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
0-9	2	5	7	1	0	1	1	0	1	1	0	1	0	0	0
10-19	15	1	16	0	1	1	0	2	2	0	1	1	0	0	0
20-29	39	14	53	9	5	14	4	2	6	3	2	5	1	0	1
30-39	79	17	96	16	11	27	11	11	22	1	1	2	0	0	0
40-49	50	25	75	20	13	33	14	21	35	1	0	1	0	0	0
50-59	55	30	85	26	16	42	25	35	60	5	1	6	2	0	2
60-69	30	24	54	19	7	26	26	57	83	1	3	4	1	0	1
70-79	12	10	22	13	9	22	15	22	37	1	1	2	0	0	0
80-89	1	0	1	2	3	5	2	1	3	0	0	0	0	0	0
unknown	11	9	20	12	4	16	6	4	10	0	0	0	0	0	0
Total	294	135	429	118	69	187	104	155	259	13	9	22	4	0	4
(%)	(69)	(31)		(63)	(37)		(40)	(60)		(59)	(41)		(100)	(0)	

Table 5. Hospitalized cases of Hemorrhagic fever with renal syndrome patients in the Republic of Korea

Year	Korean civilian	Korean soldiers	US soldiers	Total
1951	...	26	827	853
1952	...	18	833	851
1953	...	...	455	455
1954	19	...	307	326
1955	...	...	20	20
1956	...	26	28	54
1957	...	21	13	34
1958	...	20	15	35
1959	...	47	79	126
1960	...	185	10	195
1961	...	341	27	368
1962	...	311	29	340
1963	...	257	11	268
1964	18	205	22	245
1965	2	110	99	211
1966	11	82	36	129
1967	13	86	31	130
1968	26	102	28	156
1969	48	134	9	191
1970	131	221	13	365
1971	391	358	2	751
1972	186	203	0	389
1973	241	237	0	478
1974	176	251	0	427
1975	466	370	1	837
1976	585	304	4	893
1977	288	241	7	536
1978	207	168	10	385
1979	241	122	1	364
1980	185	72	1	258
1981	377	164	2	543
1982	378	123	3	504
1983	402	98	3	503
1984	568	156	6	730
1985	531	159	7	697
1986	530	166	14	710
1987	533	163	5	701
1988	264	97	6	367
1989	306	104	6	416
1990	964	73	6	1043
1991	1190	44	0	1234
1992	1116	49	2	1167
	10393	5914	2978	19285

Table 6. Geographical and monthly occurrence of civilian cases of Hemorrhagic fever with renal syndrome confirmed from sera submitted to Institute of Viral Disease, Korea University in 1992.

Province	Month												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Seoul city	7	7	5	13	20	16	9	12	6	16	15	18	144
Kyounggi-do	8	9	6	6	3	5	9	9	6	29	63	39	192
Kangwon-do	0	1	1	0	1	1	5	3	0	6	3	3	24
Chungcheongbuk-do	1	1	1	0	0	1	1	2	0	0	3	3	13
Chungcheongnam-do	1	0	0	0	1	5	1	0	1	3	4	0	16
Kyungsangbuk-do	0	0	0	0	0	0	0	0	0	0	1	0	1
Kyungsangnam-do	0	0	0	0	0	0	1	0	0	0	0	0	1
Jeollabuk-do	2	0	0	0	0	0	0	0	0	0	0	1	3
Jeollanam-do	0	0	0	0	2	0	0	0	0	0	3	3	8
Jeju-do	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	3	1	1	3	5	2	0	1	1	7	1	2	27
Total	22	19	14	22	32	30	26	27	14	61	93	69	429

Table 7. Occurrence of civilian cases of Hemorrhagic fever with renal syndrome in districts of Seoul city confirmed from sera submitted to Institute of Viral Disease, Korea University in 1992.

District	Number	District	Number
Yongsan-ku	5	Joong-ku	3
Seongbuk-ku	12	Jungryang-ku	6
Seongdong-ku	11	Kwanak-ku	8
Yeongdeungpo-ku	5	Songpa-ku	3
Dobong-ku	23	Eunpyung-ku	6
Dondaemun-ku	7	Kangseo-ku	6
Kuro-ku	12	Mapo-ku	6
chongro-ku	2	Seocho-ku	3
Dongzak-ku	7	Seodaemun-ku	3
Kangdong-ku	4	Kangnam-ku	1
Nowon-ku	3	Yangcheon-ku	8
Total	144		

Table 8. Prevalence of antibodies to scrub and murine typhus in specimens from Chinhae and Koje Island hospitals, 1991-2.

		scrub			murine		
Hospital	n	pos	(%)	p	pos	(%)	p
Chinhae Jeil	653	46	(7)		151	(23)	
				<0.001			0.04
Chinhae Hyundai	71	15	(21)		25	(35)	
Koje Daewoo	324	77	(24)		91	(28)	
				0.01			0.2
Koje Christian	216	31	(14)		72	(33)	
overall	1264	169	(13)		339	(27)	